An update on the molecular pathology of the intestinal polyposis syndromes

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Abstract

The intestinal polyposis syndromes are characterised by multiple polyps of the large bowel, increased risk of colorectal cancer and a variety of extra-colonic manifestations. Most are caused by high-penetrance germline mutations in genes that affect signalling pathways (Wnt, BMP or mTOR) or the repair of base substitution mutations. However, there are exceptions to these rules: Lynch syndrome usually presents with few polyps; and hyperplastic (serrated) polyposis currently has no known genetic cause. Polyp morphology also varies considerably between, and sometimes within, syndromes. Patients with the same germline mutations can have very different disease severities and features, perhaps as a result of modifying genes or simply chance. Although clinical features and histopathology will continue to have an important role, molecular testing is best placed to classify these diseases and hence inform patient management. As more genes are identified, this classification is likely to improve and enable better individual cancer prevention based on the mutated gene, the specific germline mutation, modifier genes and non-genetic factors.

Keywords colorectal cancer; DNA repair; genetics; polyposis; Wnt and BMP signalling

Introduction

The colorectal polyp is accepted as being the precursor lesion for most cancers of the large intestine. These polyps usually take the form of conventional adenomas or a variety of lesions with serrated morphology, some of which take a sessile form. However, there also exist a small number of rare, inherited conditions in which there is a primary, high-penetrance predisposition to intestinal polyps caused by a single faulty gene. In some of these polyposis syndromes, the primary predisposition is to conventional adenomas and in others it is to serrated lesions, yet in other inherited polyposes, polyps are seen that very rarely have any counterpart in the general population. Furthermore, in most of the polyposis syndromes, polyps are not confined to the large bowel, and there also often exist specific extra-intestinal features that can help in the diagnosis of these conditions. Almost without exception, the risk of colorectal carcinoma is increased in the polyposis syndromes, but the risk of other specific extra-colonic cancers is also raised in most cases, albeit rarely to a lifetime risk as high as that of colorectal cancer.

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Conflicts of interest: none declared.

In this short review, I shall take a tour through the molecular pathology of the major, known polyposis syndromes (Table 1), focussing on recent new findings.

Familial adenomatous polyposis (FAP)

FAP is caused by germline mutations in the APC gene (chromosome 5p22.1) which encodes a protein with a major isoform of 2843 amino acids. The protein is multi-functional, but its main role seem to be to provide a scaffold for the phosphorylation of the Wnt pathway effector, β-catenin which is subsequently degraded.[1] With very few exceptions, pathogenic *APC* mutations are protein-truncating or -ablating mutations that disrupt the scaffold. The great majority of pathogenic mutations occur before codon 1580, and thereby remove critical "SAMP" repeats that bind β-catenin. Simple base substitution mutations are almost all non-pathogenic, although splice-site mutations can be. Classical FAP is a disease of 100s—1000s of adenomatous polyps throughout the colorectum, although an attenuated disease variant — caused by germline mutations in the ends of the gene or the alternatively spliced exon 9 — also exist and patients develop fewer polyps, typically 10—100. In addition, there exist more subtle associations between polyp burden and *APC* mutation location.[2] As well as colorectal adenomas and CRC, FAP patients are at increased risk of duodenal polyps and carcinoma, gastric polyps, intra-abdominal desmoids and congenital hypertrophy of the retinal pigment epithelium (CHRPE), and also have modestly increased risks of thyroid cancer, hepatoblastoma, adrenocortical carcinoma and brain tumours.

APC is a prototypical tumour suppressor gene and FAP polyps generally start to grow after "second hits" inactivate the wildtype allele,[3] although many FAP polyps are polyclonal, comprising cells with different, independent second hits.[4] The APC mutations are thought to provide a very modest selective advantage to the adenoma cell, but this is sufficient to cause thousands of polyps given the huge number of crypts in the colorectum.[5] Hundreds or more adenomas generally occur in the teens, but few progress to CRC before the age of 30. In most cases, colectomy or more extensive surgery is required to control the disease, but this leaves considerable morbidity and risk of death from duodenal carcinoma or desmoid disease.[6]

Despite the hypothetical constitutive Wnt activation that bi-allelic inactivation of APC causes, the level of β-catenin in FAP polyps is not always obviously raised and the protein is not always present in the nucleus where it can effect transcription.[7] Although the epithelium is *APC*-mutant, it is possible that the wildtype mesenchyme can partly constrain the growth of FAP polyps through production of homoeostatic growth signals, or that the Wnt increase potentially delivered by *APC* mutation is buffered by cell-intrinsic mechanisms. Nonetheless, when CRCs occur in FAP, they have generally followed a classical pathway in which *APC* mutations are followed by mutations in genes such as *KRAS*, *SMAD4* and *TP53*, probably accompanied by a grossly abnormal chromosome complement (CIN).

The major remaining scientific and clinical challenges in FAP include gaining a full understanding of how *APC* mutations cause tumours, especially whether functional consequences other than Wnt activation are important, and developing effective therapies against desmoids, which are benign, yet very

A summary of the colorectal polyposis syndromes

Condition	Gene	Colonic features	Extra-colonic features	Polyp morphology	Mechanism
Familial adenomatous polyposis (FAP)	APC	Multiple polyps, carcinoma	Duodenal polyps and cancer, gastric polyps, intra-abdominal desmoids, Gardners', CHRPE, thyroid cancer, hepatoblastoma	Classical adenoma	Wnt activation
MUYTH-associated polyposis (MAP)	MUYTH	Multiple polyps, carcinoma	Duodenal polyps and cancer, gastric polyps	Classical adenoma Possibly serrated polyps	Defective base excision repair
Polymerase proofreading-associated polyposis (PPAP)	POLE POLD1	Multiple polyps, carcinoma	Duodenal polyps and cancer, endometrial cancer, possibly other cancers	Classical adenoma	Defective polymerase proofreading repair
Juvenile polyposis (JPS)	SMAD4 BMPR1A	Multiple polyps, carcinoma	Duodenal polyps, gastric polyps. AV malformations with SMAD4 mutations	Juvenile-type (smooth, lobulated, cystic)	BMP inhibition
Hereditary Mixed Polyposis (HMPS)	GREM1	Multiple polyps, carcinoma	None known	Several different types and mixed morphology Hyperplastic polyps and serrated adenomas predominate	BMP inhibition
Cowden syndrome (CS)	PTEN	Multiple polyps Carcinoma risk unclear	Many	Hamartomas, juvenile-like	AKT activation
Peutz–Jeghers syndrome (PJS)	LKB1 (STK11)	Multiple polyps, carcinoma	Polyps elsewhere in gastrointestinal tract Risk of several other cancer types "Freckling" of lips, buccal mucosa and other skin sites	PJS-type (arborizing, smooth muscle core)	mTOR activation
Hyperplastic polyposis (HPPS)	Not known	Multiple polyps, carcinoma	None known	Hyperplastic polyps (often large, proximal colon), serrated and conventional adenomas	Not known
Multiple adenomas (MAs)	Not known Polygenic in some cases	Multiple polyps, carcinoma	None known	Classical adenomas, sometimes with serrated lesions	Not known

Table 1

difficult to eradicate with surgery, and the cause of very dangerous side-effects owing to their size and effects on nearby organs.

DNA repair deficiencies: Lynch syndrome, polymerase proofreading-associated polyposis and MUTYH-associated polyposis

These conditions have related causes in a compromised ability to repair mispaired bases or small insertion-deletion mutations, often arising from DNA replication errors. Lynch syndrome (LS) results from defective DNA mismatch repair (MMR). A germline MMR mutation in *MSH2* (chromosome 2p21, including deletions overlapping with the *EPCAM* gene), *MLH1* (chromosome 3p21.3), *MSH6* (chromosome 2p16.3) or *PMS2* (chromosome 7p22.1) causes MMR inactivation once a second hit occurs. LS is typified by CRC, endometrial cancer and lower, risks of other cancers (gastric, ovarian, skin (Muir–Torre syndrome), small bowel, uroepithelial, and others),[8] but usually there is no true polyposis; however, a few LS patients do develop multiple serrated polyps or adenomas,[9] for reasons that are not well understood, but may include the action of modifying genes. MMR acts after normal DNA replication to "mop up" spontaneous mutations that have eluded other repair mechanisms after a cell replicates its DNA. It is relatively more effective against small insertions or deletions, and here its loss causes the phenomenon of "microsatellite instability" (MSI) in short repeat tracts. It has been shown that the colons of LS patients contain multiple crypts that have lost MMR after second hits, but – in contrast to FAP – these crypts do not generally turn into a tumour and LS cases overall have a very modest excess of polyps.[10] However, when tumorigenesis does occur, it appears to be very rapid in LS, with endoscopically-visible lesions having a short life before progression, again in contrast to FAP.

Polymerase proofreading-associated polyposis (PPAP) is a recently described, autosomal dominant condition that is functionally related to LS. The defect in PPAP is in the first stage (prior to MMR acting) in correcting errors from DNA replication. The major DNA polymerases (ε and δ) have a polymerase domain, and a proof-reading (exonuclease) domain, and PPAP patients have defects in the latter that cause a massive accumulation of base substitution mutations. Specific, germline missense mutations in the *POLE* (chromosome 12q24.33) and *POLD1* (chromosome 19q13.33) genes cause proof-reading deficiency and tumorigenesis.[11] The PPAP phenotype is like LS in its tumour spectrum, but often with multiple colorectal adenomas (like attenuated polyposis) and usually without MSI. PPAP cancers seem not to have second hits at *POLE* or *POLD1*, and are thought to have acquired millions of mutations.

MUTYH-associated polyposis (MAP) is unusual in the polyposis syndromes in that it is inherited as a recessive trait. It was discovered when researchers were investigating patients with a phenotype very like attenuated FAP. The polyps of the patients being studied had no identifiable germline cause for their disease, but the somatic *APC* mutation spectrum was unusually biased towards G:C > T:A changes, indicating a defect in DNA base excision repair. Bi-allelic mutations in *MUTYH*, a gene that encodes a DNA glycosylase involved in fixing oxidative damage by base excision repair, were found in the patients.[12] Very recently, consanguineous individuals with a phenotype resembling LS, MAP and PPAP have been reported to carry homozygous inactivating germline mutations in another base excision repair gene, *NTHL1*. The pathogenesis of these tumours is likely to result from similar mechanisms to those in MAP.[29]

Furthermore, there exists a very rare set of patients with bi-allelic germline mutations in the MMR genes. These individuals have "congenital MMR deficiency" (CMMRD), and often present with early-onset brain tumours or leukaemias. However, a small number of patients have multiple colorectal adenomas. Paradoxically, CMMRD tumours are often MSI-negative, but colorectal adenomas appear to be able to readily progress to cancer, the most severely affected individual in the literature having a total of 10 CRCs at age 23.[13] Interestingly, brain tumours in CMMRD patients seem to develop by acquiring very similar POLE and POLD1 mutations to those found in PPAP, rather than directly through MMR deficiency.[14]

There is currently little indication as to why different, yet functionally related, forms of DNA repair defect confer overlapping, but distinct, phenotypes and different modes of inheritance. There are some clues. For example, it is suspected that the MMR mutations in CMMRD do not cause severe constitutional loss of MMR capability, or they would be developmentally lethal, but why they do not cause MSI is very unclear. One possibility is that they actually have only partial MMR loss, as evidenced by the preponderance of *PMS2* and *MSH6* mutations in these cases, rather than the *MSH2* and *MLH1* mutations more typical of LS.

The hamartomatous polyposis syndromes: juvenile polyposis, hereditary mixed polyposis, Cowden syndrome and Peutz—Jeghers disease

Hamartomas are classically an excess of normal tissue, although it is not clear that this classification is appropriate for the hamartomatous polyposes except inasmuch as the polyps are mostly non-dysplastic. In all the above cases, it remains uncertain whether these lesions arise from clonal expansion of a single cell or few cells, or whether they are the offspring of multiple cells. It is also debated whether these genes act as tumour suppressors (with inactivation of the germline wildtype allele in polyps) and even whether the underlying defect is in the epithelium or mesenchyme. However, it is clear that juvenile polyposis (JPS) and Peutz—Jeghers syndrome (PJS), at least, are associated with a greatly increased risk of colorectal carcinoma. All the hamartomatous polyposes are dominantly inherited conditions and they often present in childhood.

JPS polyps are classically smooth and lobulated, with a cystic appearance and predominant stroma. They can occur throughout the gastrointestinal tract and can cause cancers of the stomach, small bowel and colorectum. The cancer risk per polyp is probably higher than in FAP. Germline mutations in two genes, *SMAD4* (chromosome 18q21) and *BMPR1A* (chromosome 10q23.2), can cause JPS.[15,16] Patients usually present with a mixture of juvenile and adenomatous polyps. *SMAD4* mutations are associated with more severe upper gastrointestinal disease[17] and, in some families, with arterio-venous malformations that can result in hereditary haemorrhagic telangiectasia.[18] Both SMAD4 and BMPR1A act in the bone morphogenetic protein signalling (BMP) pathway, which is related to the TGF-beta pathway. BMP signalling is thought to be a pro-differentiation force in the normal intestinal crypt, and its attenuation by germline mutation may favour proliferation and/or a stem cell phenotype.[19]

Hereditary mixed polyposis syndrome (HMPS) results from another germline BMP pathway defect, specifically overexpression of the secreted BMP antagonist GREM1. The HMPS mutation appears to have arisen from a single ancestor and to date HMPS has only been reported in individuals of Ashkenazi Jewish descent. The actual mutation is an unusual 40 kb duplication upstream of *GREM1* (chromosome 15q13.3) which causes the protein to be produced not only in the crypt mesenchyme, but also in the epithelium.[20] HMPS polyps can resemble hyperplastic/serrated lesions, conventional adenomas or juvenile polyps, with multiple morphologies often present in the same lesion. Uniquely among the Mendelian CRC syndromes, HMPS has no known extra-colonic features.

Cowden syndrome (CS), and its variants Lhermitte—Duclos and Bannayan—Zonana—Riley—Ruvalcaba—Myhre—Smith syndromes, is sometimes termed the multiple hamartoma syndrome. It is a complex disorder with many variable features, including polyps of the large bowel that resemble juvenile polyps and increased breast, thyroid and endometrial cancer risk. It is very unusual for CS to present with bowel polyps alone and the risk of bowel cancer in CS cases is also uncertain.[21] The genetics of CS are no less confusing and controversial, but it is firmly established that germline *PTEN* mutations are the major cause.[22] *PTEN* (chromosome 10q23.3) normally acts to repress Pi3 kinase and AKT signalling.

PJS has features that, aside from a greatly raised colorectal cancer risk and dominant inheritance, overlap minimally with those of the other Mendelian CRC syndromes. PJS polyps can occur throughout the gastrointestinal tract and even in other epithelia, such as the nose. They are classically arborizing lesions

with a prominent smooth muscle core and stalk. PJS patients have a greatly increased risk of CRC, but also have raised risks of cancers of many other sites, including the stomach, breast, pancreas, gall bladder and endometrium.[23] The other classical feature of PJS is pigmentation of the lips, buccal mucosa and often other skins areas: these lesions resemble dark freckles and are said to result from a failure to transfer melanin from melanocytes to keratinocytes. The pigmentation in PJS tends to fade with age, can be very variable in severity, and can resemble several other syndromes that are not associated with increased cancer risk. The PJS gene (*STK11*, otherwise known as *LKB1*) maps to chromosome 19p13.3 and encodes a protein that acts in the mTOR signalling pathway.[24,25] It is probably is an upstream kinase of the major energy sensor AMPK, and the mechanism of action of *LKB1* mutations, whilst largely unclear, seem different from any of the other polyposis genes.

Diagnosis of the Mendelian polyposis syndromes

The availability of rapid, sensitive and specific methods of DNA sequencing mean that the classification of the polyposis syndromes is now primarily molecular. Screening panels for all the genes described above are available and are being introduced into clinical practice. Occasionally, where there is excellent clinical and family history evidence, and where the mutation spectrum is restricted, focussed screening can be performed first. For example, an Ashkenazi individual with a dominant family history and polyps with mixed morphology can be screened for HMPS using a single polymerase chain reaction (PCR); and MAP can be rapidly screened using one or two PCR reactions for the most common mutations in specific ethnic groups. However, these methods are slowly being displaced, especially as we come to realise that most inherited cancer syndromes confer not only very high risks of some cancers, but also small increased risks of several other cancer types.

Even where no mutation can be found, molecular methods can be used to diagnose some polyposis syndromes. LS cancers have MSI and often show loss of the MMR protein(s) on immunohistochemistry; they can be distinguished from sporadic MSI + cancers by a lack of MLH1 methylation and, usually, absence of *BRAF* mutation. These tests can also help to sort pathogenic mutations from rare bystander mutations. Mutation burden and spectrum tests in polyps can also be used in principle to diagnose MAP and PPAP, although these tests are not routinely used in clinical molecular practice.

There will remain some patients with occult mutations, or mutations in undiscovered predisposition genes, who must be classified using their clinical features, family history and histopathology. The accuracy of this is likely to be highly variable. For example, patients with thousands of colorectal adenomas, desmoids and a dominant family history are likely to have FAP, whereas those with arborizing polyps and buccal pigmentation are likely to have PJS. However, other patients are much harder to classify, as the following section shows.

The genetically uncharacterised polyposes: hyperplastic polyposis syndrome and the multiple adenoma phenotype

Hyperplastic polyposis syndrome (HPPS, or serrated polyposis syndrome) is a poorly defined condition with uncertain inheritance.[26] At one extreme, there exist patients with tens of hundreds of serrated polyps that present in their 20s or 20s and who may also have CRC. Extra-colonic disease is rare and usually there are few, if any, affected relatives. It is unclear whether this condition is distinct from, or continuous with, the phenotype of asymptomatic older patients found to have tens of small serrated polyps, often in bowel cancer screening programmes. The definition of HPPS is evolving to take account of age, polyp sites and burden, and the presence of CRC, but what is ultimately required is a molecular classification.[27] Unfortunately, with the exception of a very few patients with germline *MUTYH* or *GREM1* mutations, HPPS predisposition genes have not been forthcoming despite tens of patients having had exome sequencing for germline mutations. Several potential explanations exist for this failure (for example, occult mutations and even a non-genetic aetiology). The HPPS phenotype may overlap with that of a second group of patients with multiple colorectal adenomas (MAs), but no mutations in the known Mendelian CRC genes. MA patients too can present in the first 2 or 3 decades of life with hundreds of conventional adenomas, CRC and often very limited family history. As for HPPS, MA genes have in general not been forthcoming in large sequencing projects, although PPAP and *NTHL1*-associated polyposis were discovered in that way. It is quite possible that both HPPS and MA are severely genetically heterogeneous and that even larger sequencing efforts will be needed to characterise them genetically. There is also some evidence that some HPPS and MA cases represent individuals in the tail of the normal distribution of common, low-risk CRC predisposition polymorphisms.[28]

Concluding remarks

The polyposis syndromes are fascinating examples of how cancers can arise in a number of different settings. Polyp morphology is shared across some syndromes (FAP, AFAP, MAP, PPAP), but not others, the cancer risk is variable, and often hard to estimate, and the presence of extra-colonic features differs among patients and genes. Most polyposis syndromes are high-penetrance, Mendelian dominant conditions, with the exception of MAP and *NTHL1*-associated polyposis, and perhaps, HPPS. Most of these diseases can be detected in childhood, either owing to a known family history, classical phenotype (for example, FAP), or sometimes owing to unusual presentations (such as intussusception or volvulus caused by polyps in PJS). However, new cases of PPAP and MAP are more often detected in adults. There are many molecular ways to cause a polyp, including DNA repair deficiency and signalling pathway activation or abrogation, and identical phenotypes can be caused by very different underlying defects, such as Wnt activation in FAP and DNA repair problems in MAP and PPAP. Furthermore, it is very unclear as to why the DNA repair defects involved in CRC predisposition are principally those in which single base changes are corrected. We also need to explain why LS does not usually present with multiple polyps — in contrast to MAP, PPAP, CMMRD and *NTHL1*-associated polyposis — although this is likely in part to reflect the need for "second hits" to inactivate the wildtype copy of *MSH2* and *MLH1*. Finally, it is now the case that molecular testing is best placed to classify these diseases and hence inform patient management. As time goes on, this

classification will improve and enable cancer prevention measures increasingly to be tailored to individuals. ◆

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Acknowledgements

Core funding to the Wellcome Trust Centre for Human Genetics was provided by the Wellcome Trust (090532/Z/09/Z). I am also grateful to the EU COST Action BM1206 on colorectal cancer genetics.